Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/000978

International filing date: 01 February 2005 (01.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0402262.0
Filing date: 02 February 2004 (02.02.2004)

Date of receipt at the International Bureau: 10 March 2005 (10.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

PCT/EP2005/000978

INVESTOR IN PEOPLE

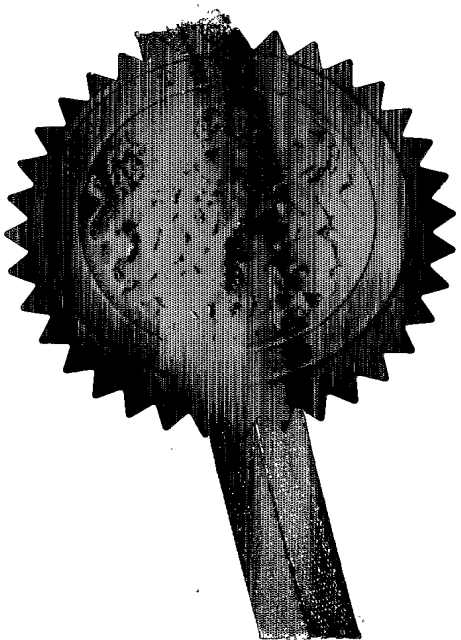
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed Andrew Gray

Dated 4 January 2005

Patents Form 1/77

Patents Act 1977
(Rule 16)

The **Patent Office**

THE PATENT OFFICE
C
- 2 FEB 2004
LONDON

03FEB04 E870116-5 000245
P01/7700 0.00-0402262.0 ACCOUNT CHA

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1.	Your reference	**4-33615P1**
2.	Patent application number *(The Patent Office will fill in this part)*	02 FEB 2004 **0402262.0**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	7125470001
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Process for the Manufacture of Organic Compounds**
5.	Name of your agent *(If you have one)*	**Craig McLean**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**Novartis Pharmaceuticals UK Limited** **Patents and Trademarks** **Wimblehurst Road** **Horsham, West Sussex** **RH12 5AB** ✓
	Patents ADP number *(if you know it)*	**07181522002**

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	20
Claim(s)	4
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 2nd February 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew (01403) 323069

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

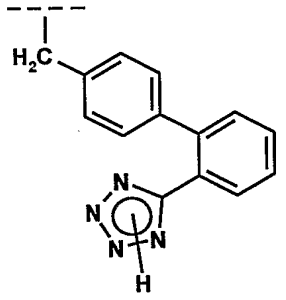
e) *For details of the fee and ways to pay please contact the Patent Office.*

Process for the Manufacture of Organic Compounds

The present invention relates to a process for the manufacture of intermediates that may be used for the manufacture of ARBs (also called angiotension II receptor antagonist or AT_1 receptor antagonist) comprising as structural feature a tetrazole ring. ARBs can, for example, be used for the treatment of hypertension and related diseases and conditions.

For example, mention may be made of ARBs that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP 253310), candesartan (cf. EP 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP 454511), olmesartan (cf. EP 503785), and tasosartan (cf. EP 539086), or, in each case, a pharmaceutically acceptable salt thereof.

All of these ARBs comprise the following common structural element:



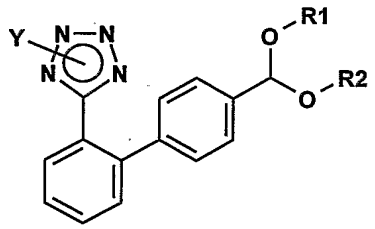
A.

The manufacture of an aldehyde corresponding to said element is a critical step in the manufacture of the above-mentioned angiotensin II receptor antagonists. Various biaryl coupling reactions have been recommended in the art.

EP 550313 describes the preparation of protected 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde involving transition metal catalyzed coupling of protected 5-(2-iodophenyl)-2H-tetrazole with an organozinc reagent or an arylboronic acid. The formation of stoichiometric quantities of zinc salt waste in the first case, and the several chemical steps required for the preparation of the arylboronic acid in the second case, and the formation of stoichiometric quantities of iodide waste in both cases are regarded as disadvantages.

US 5468867 discloses the preparation of protected 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde involving metallation with an organometallic base such as an alkyllithium reagent. A disadvantage of this procedure is the formation of stoichiometric quantities of reactive, halogen containing waste.

The objective of the present invention is to provide a novel synthesis for compounds of formula (I)



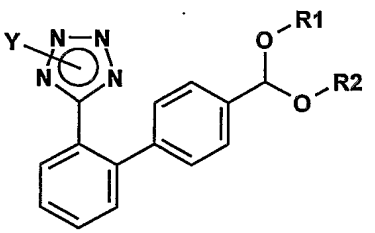
(I),

wherein Y is a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene;
that (1) does not have the disadvantages described above, (2) allows for the use of such tetrazole protecting groups which are easily removed in the presence of a Bronsted acid, (3) does not require large excesses of reagents, (4) gives high yields, (5) gives a minimum of waste, especially no stoichiometric amounts of reactive or environmentally problematic waste and (6) is economically attractive.

Compounds of formula (I) are important intermediates for the manufacture of ARBs having the structural feature A.

It has surprisingly been found that the process according to the present invention meets at least the above objectives.

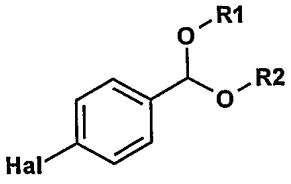
The present invention relates to a process for the manufacture of the compound of formula (I)



(I),

wherein Y represents a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene; comprising

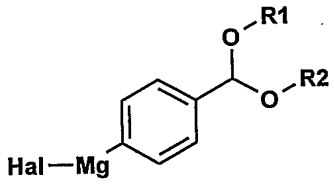
(a) reacting a compound of formula



(II a)

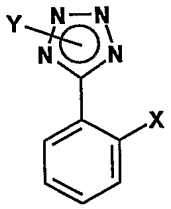
wherein Hal is chlorine, bromine or iodine, with an active form of magnesium in an appropriate solvent

(b) reacting a resulting aryl magnesium halide compound of formula



(II b)

in the presence of a transition metal catalyst and in the presence of a catalytically effective amount of a metal salt additive with a compound of formula (II c)



(II c),

wherein X is a substituent which, when bound to a phenyl ring, is not considerably replaceable at room temperature by an arylmagnesium halide reagent of formula (II b) in the absence of a catalyst; and, if necessary,

isolating a resulting compound of formula (I).

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10°C to about +140°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

A tetrazole protecting group (Y) is, for example, selected from the group consisting of tert-C_4-C_7-alkyl such as tert-butyl; methyl that is substituted by one, two or three substituents selected from C_1-C_7-alkyl and C_1-C_7-alkoxy, for example 1-ethoxyethyl, 1-methoxy-1-methylethyl; 2-tetrahydropyranyl; 2-tetrahydrofuranyl; C_1-C_2-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl or trityl, wherein the phenyl ring is unsubstituted or substituted by one or more, e.g. two or three, substituents e.g. those selected from the group consisting of tert-C_1-C_7-alkyl, C_1-C_7-alkoxy, C_2-C_8-alkanoyloxy; piperonyl; 1-methyl-1-phenylethyl; fluorenyl; methylthiomethyl; silyl such as tri-C_1-C_4-alkyl-silyl, for example, trimethylsilyl, triethylsilyl or tert-butyl-dimethylsilyl, or di-C_1-C_4-alkyl-phenyl-silyl, for example, dimethyl-phenylsilyl; C_1-C_7-alkyl-sulphonyl; arylsulphonyl such as phenylsulphonyl wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, substituents e.g. those selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkoxy, C_2-C_8-alkanoyl-oxy; C_2-C_8-alkanoyl such as acetyl or valeroyl; and esterified carboxy such as C_1-C_7-alkoxy-carbonyl, for example, methoxy-, ethoxy- or tert-butyloxy-carbonyl. Likewise, a tetrazole protecting group (Y) also may be a cation, e.g. of an alkali metal or an earth alkali metal, for example Li(I), Na(I), K(I), Rb(I), Cs(I), Mg(II), Ca(II) and Sr(II).

Examples of preferred protecting groups Y are tert-butyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, 1-methyl-1-phenylethyl, triphenylmethyl, (p-methoxyphenyl)-diphenylmethyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, 1-butoxyethyl, 1-ethoxyethyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, 1-methoxy-1-methylethyl, 1-methoxy-cyclohexyl, 1-ethoxycyclohexyl, trimethylsilyl and triethylsilyl.

Particularly preferred protecting groups Y are 1-butoxyethyl, 1-ethoxyethyl and 2-tetrahydropyranyl.

The general terms used hereinbefore and hereinafter have the following meanings, unless defined otherwise:

C_1-C_{10}-Alkyl is, for example, C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl residue. C_1-C_4-alkyl, especially methyl or ethyl, is preferred.

C_2-C_{10}-Alkylene is, for example, C_2-C_6-alkylene, such as ethylene, propylene, butylene, 1,2-dimethylethylene, 2,2-dimethylpropylene, or 1,4-dimethyl-1,4-butylene. C_2-C_4-Alkylene, especially, ethylene or propylene, is preferred.

Hal represents in particular chlorine and bromine.

C_1-C_7-Alkoxy is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, iso-butyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy, or heptyloxy residue. C_1-C_4-alkoxy is preferred. Especially preferred is methoxy, ethoxy and butoxy.

C_2-C_8-Alkanoyl is, for example, C_2-C_5-alkanoyl such as acetyl, propionyl, butyryl, valeroyl, or pivaloyl. Especially preferred is acetyl.

Step (a):

An active form of magnesium is, for example, magnesium turnings of the type normally used for such transformations, magnesium chips, magnesium powder or magnesium rods.

Furthermore, an active form of magnesium is magnesium that is activated by a catalytic amount of iodine, bromine, 1,2-dibromoethane, a hydride reagent or the arylmagnesium halide reagent intended to be prepared.

A suitable amount of magnesium is 1.0 to 1.8 molar equivalents, preferably 1.0 to 1.2 molar equivalents, with respect to the amount of compound of formula (II a) used.

The reaction is carried out, for example, in a suitable inert solvent or a mixture of solvents. Inert solvents conventionally do not react with the corresponding starting materials of formula (II a). Appropriate solvents are ethereal solvents, such as ethyl ether, tert-butyl methyl ether, tetrahydrofuran, butyl ether, 1,2-dimethoxyethane or 1,2-diethoxyethane, or a mixture of two or more of these solvents, or a mixture of one of these solvents and an aromatic solvent such as toluene or xylene. A preferred solvent is tetrahydrofuran.

A suitable reaction temperature preferably is between 0° and 75°C, preferably between 10° and 35°C.

Step (b):

The coupling step (b) is carried out in the presence of a transition metal catalyst.

A suitable transition metal is, for example, nickel, palladium, platinum, cobalt, manganese or copper. A useful transition metal salt is, for example, a nickel(II), palladium(II), platinum(II), cobalt(II), manganese(II), copper(I) or copper (II) salt such as the chloride, bromide, iodide, hydroxide, oxide, acetate, hydroxyacetate, propionate, succinate, trifluoroacetate, acetylacetonate, nitrate, cyanide, sulfate, trifluoromethanesulfonate, methanesulfonate, benzenesulfonate or p-toluenesulfonate thereof.

A suitable transition metal catalyst is preferably a complex of a transition metal or a transition metal salt and one, two or up to four coordinating ligands. The transition metal catalyst may be preformed or generated in the reaction mixture. A suitable transition metal catalyst may also be the uncomplexed transition metal in its elemental form or an uncomplexed transition metal salt. The uncomplexed transition metal or its salt may be supported on carbon, silica, alumina or diatomaceous earth.

Suitable ligands are olefins, such as 1,5-cyclooctadiene; tri(C_1-C_4-alkyl)amines, such as triethylamine and ethyl-diisopropylamine; N-C_1-C_4-alkyl-piperidines, such as N-methyl-piperidine; N,N,N',N'-tetramethylethylenediamine; heterocyclic amines and diamines, such as pyridine, N-methylimidazole, 2,2'-dipyridyl, 1,10-phenanthroline, wherein the ring is un-substituted or substituted by one or more, e.g. two or three, C_1-C_4-alkyl-residues, as for example in collidine; linear and cyclic ethers containing two or more, e.g. three or four, oxygen atoms, such as 1,2-dimethoxyethane, 1,2-diethoxyethane, di(ethylene glycol) dimethyl ether and 1,2-dimethoxybenzene.

Particularly suitable ligands are those containing one or two trivalent phosphorus atoms, for example, triphenylphosphine, tri(ortho-tolyl)phosphine and tri(para-tolyl)phosphine, tri(C_1-C_8-alkyl)phosphines such as trimethylphosphine, triethylphosphine, tributylphosphine, tri(1,1-dimethylethyl)phosphine, tri(C_4-C_7-cycloalkyl)phosphines such as tricyclopentylphosphine and tricyclohexylphosphine, tri(C_1-C_6-alkyl)phosphites such as trimethylphosphite, triethylphosphite and tri(1-methylethyl)phosphite, tri(C_4-C_7-cycloalkyl)phosphites such as tricyclopentylphosphite and tricyclohexylphosphite, and 1,2-bis(diphenylphosphino)ethane (i.e. dppe), 1,3-bis(diphenylphosphino)propane (i.e. dppp), 1,4-bis(diphenylphosphino)butane

(i.e. dppb), 1,1'-bis(diphenylphosphino)ferrocene (i.e. dppf), 1,1'-bis(di-[2-propyl]-phosphino)ferrocene, 1,1'-bis(di-tert-butyl-phosphino)ferrocene, 1,2-bis(diphenylphosphino)benzene, 2,2'-bis(diphenylphosphino)-1,1'-biphenyl (i.e. BIPHEP), 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (i.e. BINAP), bis(2-diphenylphosphinophenyl)ether (i.e. DPEphos), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (i.e. XANTHPHOS).

Transition metal salts are derived from above specific transition metals.

Preferred transition metal salts are nickel(II) chloride, nickel(II) bromide and nickel(II) acetylacetonate. A particularly preferred transition metal salt is nickel(II) chloride. Preferred ligands are triphenylphosphine, 1,2-bis(diphenylphosphino)ethane (i.e. dppe), 1,3-bis(diphenylphosphino)propane (i.e. dppp), 1,1'-bis(diphenylphosphino)ferrocene (i.e. dppf). A particularly preferred ligand is 1,2-bis(diphenylphosphino)ethane (i.e. dppe).

Preferred catalysts are dichlorobis(triphenylphophine)nickel(II), dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II), dichloro[1,3-bis(diphenylphosphino)propane]nickel(II).
A particularly preferred catalyst is dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II).

The amount of nickel catalyst used is preferably between 0.05 and 2 molar% relative to N-protected tetrazole starting material (II c), preferably between 0.2 and 1.5 molar%.

Likewise preferred transition metal salts are palladium(II) chloride, palladium(II) bromide and palladium(II) acetate. A particularly preferred transition metal salt is palladium(II) chloride. Preferred ligands are triphenylphosphine, 1,3-bis(diphenylphosphino)propane (i.e. dppp), 1,1'-bis(diphenylphosphino)ferrocene (i.e. dppf). A particularly preferred ligand is 1,1'-bis(diphenylphosphino)ferrocene (i.e. dppf).

Preferred palladium catalysts are dichlorobis(triphenylphophine)palladium(II), dichloro[1,3-bis(diphenylphosphino)propane]palladium(II) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) or its dichloromethane adduct. A particularly preferred palladium catalyst is dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) or its dichloromethane adduct.

The amount of palladium catalyst used is preferably between 0.01 and 1 molar% relative to N-protected tetrazole starting material (II c), preferably between 0.05 and 0.3 molar%.

The coupling step (b) also involves a metal salt additive. The role of the metal salt additive, which is used in catalytic amounts, is to facilitate the coupling reaction. Compared to couplings with aryl-zinc reagents, the use of catalytic amounts of such a metal salt additive results in the formation of less waste. In addition, in the presence of metal salt additive, a higher conversions of starting material (II c) can be achieved. A useful metal salt additive is a copper(I), copper(II), zinc(II), silver(I), cadmium(II), mercury(II), aluminum(III), gallium(III), indium(III), tin(IV), titanium(IV) and zirconium(IV) salt. Examples of such salts are the corresponding chloride, bromide, iodide, carbonate, hydroxide, oxide, C_1-C_7-alkanoates such as the acetate and propionate, C_1-C_7-alkoxides such as the methoxide and ethoxide, trifluoroacetate, acetylacetonate, nitrate, cyanide, sulfate, trifluoromethanesulfonate, methanesulfonate, benzenesulfonate or para-toluenesulfonate.

Preferred metal salt additives are zinc(II) salts such as zinc(II) chloride and zinc(II) bromide. A particularly preferred metal salt additive is zinc(II) chloride.

The amount of metal salt additive used is preferably between 0.1 and 8 molar% relative to N-protected tetrazole starting material (II c), preferably between 0.5 and 6 molar%.

Substituent X is a substituent that is not considerably replaceable at room temperature by an arylmagnesium halide reagent of formula (II b) in the absence of a transition metal catalyst. In particular, X is, for example chlorine or bromine. A preferred substituent X is chlorine.

When X is chlorine, the preferred transition metal of the catalyst is nickel.

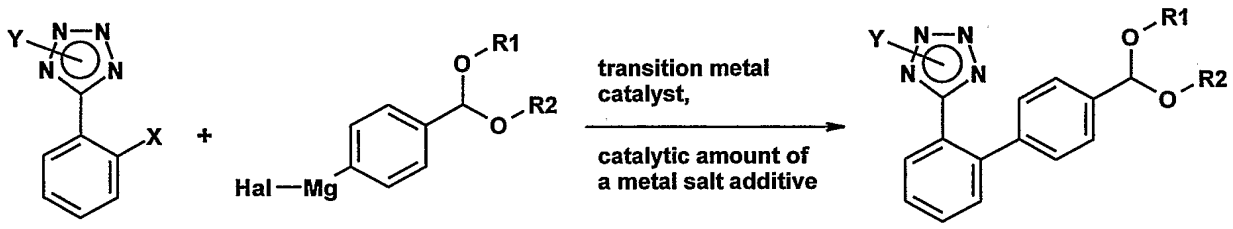
When X is bromine, the preferred transition metal of the catalyst is palladium.

Independent of the choice of catalyst, the reaction is carried out, for example, in a suitable inert solvent or a mixture of solvents. Inert solvents conventionally do not react with the corresponding starting materials of formulae (II b) and (II c).

An appropriate solvent for the reaction is an ethereal solvent, such as ethyl ether, tert-butyl methyl ether, tetrahydrofuran, butyl ether, 1,2-dimethoxyethane or 1,2-diethoxyethane; a dipolar aprotic solvent, such as 1-methyl-2-pyrrolidinone (i.e. NMP) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (i.e. DMPU); an aromatic solvent such as toluene or xylene; or a mixture of two or more solvents selected from the above groups. A preferred solvent is tetrahydrofuran.

The reaction is preferably carried out at a temperature between -10° and 60°C, preferably between 10° and 35°C.

A process for the preparation of protected 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde of formula (I) is exemplified by following reaction scheme



comprising coupling of a N-protected phenyltetrazole (X = Cl or Br; Y = tetrazole protecting group) with an arylmagnesium halide (Hal = Cl, Br, I; R_1, R_2 = C_1-C_{10}-alkyl or C_2-C_{10}-alkylene) in the presence of a transition metal catalyst, which is complexed, uncomplexed or supported nickel, palladium, platinum, cobalt, manganese or copper metal or a corresponding salt thereof, and a catalytic amount of a metal salt additive, such as a copper(I), copper(II), zinc(II), silver(I), cadmium(II), mercury(II), aluminum(III), gallium(III), indium(III), tin(IV), titanium(IV) or zirconium(IV) salt, in the presence of an inert solvent or a mixture of inert solvents.

Preferred Hal is, for example, Br.

Preferred R_1 and R_2 is, for example, methyl.

Preferred X is, for example, Cl.

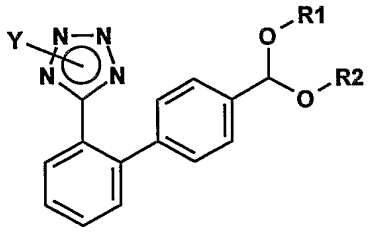
When X is chlorine, a preferred transition metal catalyst is a nickel(0) or nickel(II) complex, for example, a complex of a nickel(II) salt which is coordinated by at least one organo phosphorus compound containing trivalent phosphorus. Nickel(II) complexes comprising two organophosphorus ligands are preferred. Nickel(II) complexes with organophosphorus ligands which contain two trivalent phosphorus atoms, such as dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) (i.e. $NiCl_2$(dppe)), are particulary preferred.
A preferred metal salt additive is, for example, a zinc(II) salt such as $ZnCl_2$ and $ZnBr_2$.
Preferred solvents are ethereal solvents, particularly tetrahydrofuran.

When X is chlorine, compounds of formula (I) also can be prepared when omitting the metal salt additive (e.g. $ZnCl_2$) in above process, i.e. catalyzing the coupling reaction solely by the nickel catalyst.

When X is bromine, a preferred transition metal catalyst is a palladium complex, for example, a complex of palladium(0) or a complex of a palladium(II) salt with at least one organophosphorus compound containing trivalent phosphorus. Palladium(II) complexes comprising two organophosphorus ligands are preferred. Palladium(II) complexes with organophosphorus ligands which contain two trivalent phosphorus atoms, such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (i.e. $PdCl_2$(dppf)) or its dichloromethane adduct, are particularly preferred.
A preferred metal salt additive is, for example, a zinc(II) salt such as $ZnCl_2$ and $ZnBr_2$.
Preferred solvents are ethereal solvents, particularly tetrahydrofuran.

In a preferred embodiment of the process according to the present invention, steps a) and b) can be carried out in a one-pot reaction.

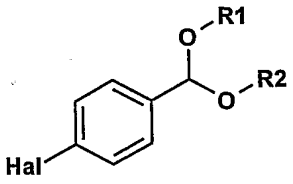
In a variation of the present invention, another embodiment of the present invention is a process for the manufacture of the compound of formula (I)



(I),

wherein Y represents a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene; comprising

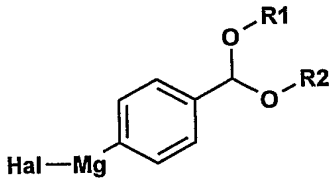
(a) reacting a compound of formula



(II a)

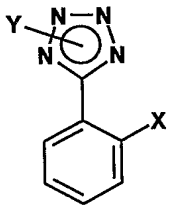
wherein Hal is chlorine, bromine or iodine, with an active form of magnesium in an appropriate solvent

(b) reacting a resulting aryl magnesium halide compound of formula



(II b)

in the presence of a transition metal catalyst with a compound of formula (II c)



(II c),

wherein X is chlorine, in the absence of a metal salt additive; and, if necessary, isolating a resulting compound of formula (I).

A further embodiment of the present invention are both reaction Steps b).

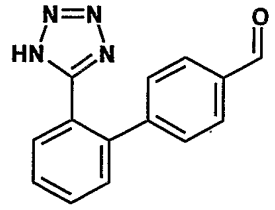
A further embodiment of the present invention is the specific reaction of a compound of formula (II b) with a compound of formula (II c), wherein X is chlorine. In the instant reaction, surprisingly, no addition of a catalytically effective amount of a metal salt additive is necessary to result in a compound of formula (I).

In the case in which both the transition metal salt and the metal salt additive are omitted, no significant amount of compound of formula (I) is formed from a starting material of formula (II c), wherein X is chlorine.

Isolation Step:

The isolation of a compound of formula (I) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (I) from the reaction mixture – if desired or necessary after work-up, especially by extraction – or by chromatography of the reaction mixture or any combined methods.

Another embodiment of this invention is combining steps (a) and (b) with a subsequent deprotection step (c) resulting in the formation of the compound of formula



(I A)

or the 2-tautomer thereof.

A resulting compound of formula (I A) is subsequently isolated.

Step (c):

For this purpose, the protecting groups of the resulting compound of formula (I) of step (b) are removed sequentially or in a single step under conditions of hydrolysis, preferably in the presence of a Bronsted acid.

Step (c) is carried out, for example, by dissolving a compound of formula (I) in water or a mixture of water and an appropriate organic solvent and subsequent treating with an acid at elevated temperature.

Appropriate organic solvents are ethers, such as tetrahydrofuran, 1,4-dioxan, butyl ether, nitriles, such as acetonitrile, alcohols, such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, isopropyl acetate, toluene, xylene, acetic acid or formic acid. Preferred solvents are methanol and ethanol.

Suitable acids are Bronsted acids, such as sulfuric acid, hydrochloric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, para-toluenesulfonic acid, benzoic acid, acetic acid, formic acid as well as polymer supported Bronsted acids (e.g. acidic ion exchange resins). Preferred acids are sulfuric acid and hydrochloric acid.

The amount of acid used is between 0.05 and 2.0 equivalents with respect to compound of formula (I), preferably between 0.1 and 1.2 equivalents.

The reaction is carried out at a temperature between 0°C and the boiling point of the solvent, preferably between 25° and 70°C.

The isolation of a compound of formula (I A) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (I A) from the reaction mixture – if desired or necessary after work-up, especially by extraction – or by chromatography of the reaction mixture or any combined methods. For example, crystallization of the product is accomplished by distilling off all or a part of the organic solvent, adding water, cooling the mixture or a combination of these measures.

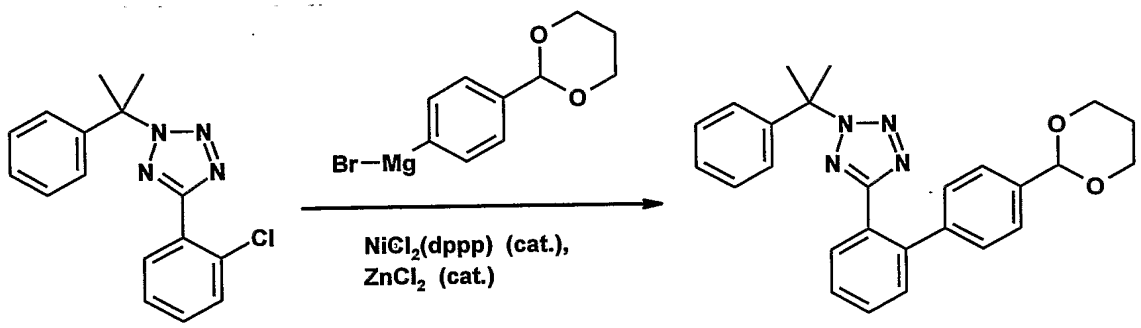
Several starting materials of formula (II a) are known in the art and can be prepared, for example, by conventional acid catalyzed acetalization of 4-bromobenzaldehyde in the presence of an alcohol or diol. For example, the preparation of compound of formula (II a) with R_1 and R_2 being methyl is described in Journal of Organic Chemistry 1991, 56, 4280. The corresponding compound with R_1 and R_2 being ethyl can be prepared in ethanol in the presence of triethyl orthoformiate and an acid catalyst.

Several starting materials of formula (II c) with different protecting groups Y are known in the art. The preparation of some examples is described in EP 788487 B1.

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner, for example, to specific reaction conditions.

Example 1:

Preparation of 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-2-(1-methyl-1-phenyl-ethyl)-2H-tetrazole



To magnesium turnings (0.882 g) are added under anhydrous conditions 12 ml of a solution of 2-(4-bromo-phenyl)-[1,3]dioxane (8.02 g; 33 mmol) in anhydrous tetrahydrofuran (33 ml). The mixture is warmed to about 50°C, and five drops of 1,2-dibromoethane are added. After the reaction starts, the mixture is heated to reflux and the remainder of the solution of 2-(4-bromo-phenyl)-[1,3]dioxane is added over 40 minutes. The resulting mixture is further stirred at 60°C for one hour and finally allowed to cool down to room temperature. The concentration of 4-([1,3]dioxan-2-yl)phenylmagnesium bromide in the solution above the excess of magnesium turnings is 0.50 M according to titration.

In another flask, dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (0.022 g; 0.04 mmol) is suspended in tert-butyl methyl ether (3 ml) and cooled to about 0°C before a 0.5 M solution of zinc chloride in tetrahydrofuran (0.40 ml; 0.20 mmol) and a solution of 5-(2-chloro-phenyl)-2-(1-methyl-1-phenyl-ethyl)-2H-tetrazole (1.20 g; 4.0 mmol) in tert-butyl methyl ether (1.2 ml) are added. To the vigorously stirred resulting suspension is added at about 0°C 9.6 ml of the above 0.5 M 4-([1,3]dioxan-2-yl)phenylmagnesium bromide solution (4.8 mmol) over one hour. The resulting dark brown solution is allowed to warm up and further stirred at room temperature for 20 hours. The mixture is cooled to about 0°C, quenched with 10 ml of a 3.8 % solution of ammonium chloride in water and diluted with ethyl acetate (25 ml). The aqueous phase is separated and extracted with ethyl acetate (25 ml). The combined organic phases are washed with a 0.5 M solution of sodium hydroxide in water (10 ml) and with a 10 % solution of sodium chloride in water (10 ml). The combined organic phases are evaporated in vacuo. A solution of the resulting pale green solid in a small amount of ethyl acetate is filtered and evaporated. The resulting pale green solid is purified by column chromatography on silica gel eluting with a 1:10 mixture of tert-butyl methyl ether and

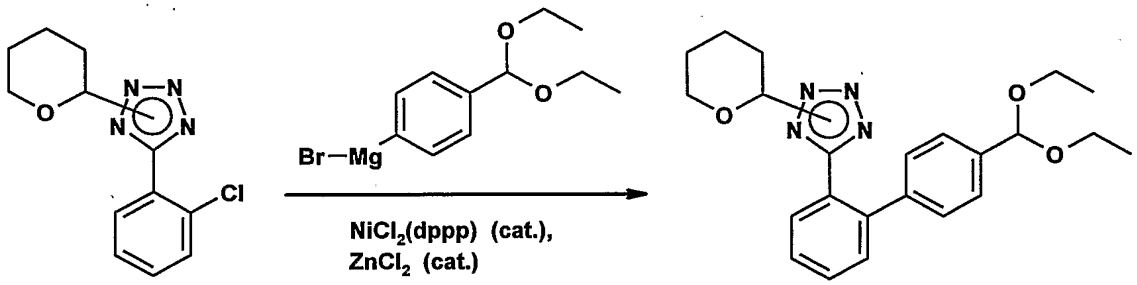
toluene to afford 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-2-(1-methyl-1-phenyl-ethyl)-2H-tetrazole as colorless crystals.

^{1}H-NMR (400 MHz, d_6-DMSO): 1.47-1.52 (m, 1 H), 2.01 (s, 6 H), 2.02-2.07 (m, 1 H), 3.96-4.02 (m, 2 H), 4.17-4.21 (m, 2 H), 5.55 (s, 1 H), 6.95-6.98 (m, 2 H), 7.10-7.13 (m, 2 H), 7.32-7.39 (m, 5 H), 7.51-7.53 (m, 1 H), 7.56-7.61 (m, 1 H), 7.65-7.69 (m, 1 H), 7.78-7.80 (m, 1 H).

Melting range: 102-106°C.

Example 2:

Preparation of 5-(4'-diethoxymethyl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole



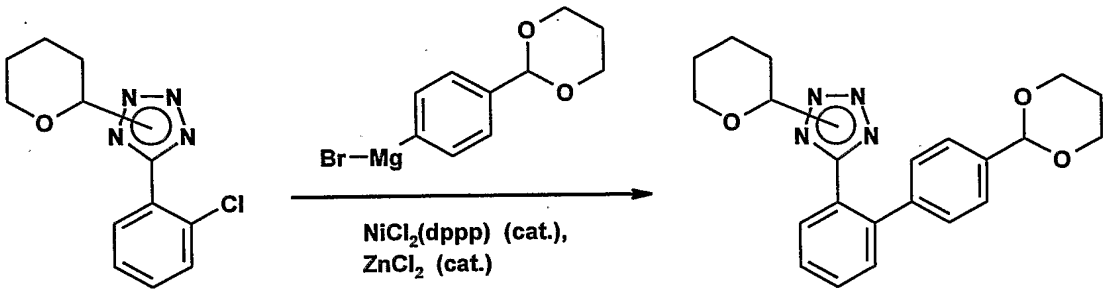
To magnesium turnings (2.92 g) is added under anhydrous conditions one fifth of a solution of 1-bromo-4-(diethoxymethyl)benzene (25.9 g; 100 mmol) in anhydrous tetrahydrofuran (80 ml). The mixture is warmed to about 40°C and 1,2-dibromoethane (0.09 ml; 1.0 mmol) is added. After the reaction starts, the remainder of the solution of 1-bromo-4-(diethoxymethyl)benzene is added over one hour. The resulting mixture is further stirred at 40°C for two hours and at room temperature for 30 minutes and is finally diluted by adding anhydrous tetrahydrofuran (25 ml). The concentration of 4-(diethoxymethyl)phenylmagnesium bromide in the solution above the excess of magnesium turnings is 0.46 M according to titration.

In another flask, dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (0.027 g; 0.05 mmol) is suspended in tert-butyl methyl ether (3.8 ml) and cooled to about 0°C before a 0.5 M solution of zinc chloride in tetrahydrofuran (0.50 ml; 0.25 mmol) and a solution of a mixture of 5-(2-chlorophenyl)-2-(tetrahydropyran-2-yl)-2H-tetrazole and 5-(2-chlorophenyl)-1-(tetrahydropyran-2-yl)-1H-tetrazole (1.32 g; 5.0 mmol) in tert-butyl methyl ether (1.3 ml) are added. To the vigorously stirred resulting suspension is added at about 0°C 13 ml of the above 0.46 M 4-(diethoxymethyl)phenylmagnesium bromide solution (6.0 mmol) over one hour. The resulting black-yellow solution is stirred at about 0°C for 5 hours, allowed to warm up and further stirred at room temperature for 19 hours. The mixture is cooled to about 0°C and quenched with a 7.5 % solution of ammonium chloride in water (10 ml). The aqueous

phase is separated and extracted with ethyl acetate (25 ml). The combined organic phases are washed with water (10 ml), a 7.5 % solution of sodium carbonate in water (10 ml) and a 10 % solution of sodium chloride in water (10 ml). The combined organic phases are evaporated in vacuo. A solution of the resulting brown-yellow oil in a small amount of ethyl acetate is filtered and evaporated. The resulting oil (2.68 g) is purified by column chromatography on silica gel eluting with a 1:4 mixture of ethyl acetate and hexane (in the presence of 0.2 volume-% of triethylamine) to afford the main isomer (N2-isomer) 5-(4'-diethoxymethyl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole as a colorless oil. ^{1}H-NMR of N2-isomer (400 MHz, $CDCl_3$): 1.24 (t, J = 7.2 Hz, 6 H), 1.60-1.67 (m, 3 H), 1.86-2.03 (m, 2 H), 2.11-2.17 (m, 1 H), 3.50-3.73 (m, 6 H), 5.49 (s, 1 H), 5.97-5.99 (m, 1 H), 7.17-7.20 (m, 2 H), 7.37-7.39 (m, 2 H), 7.43-7.56 (m, 3 H), 7.90-7.92 (m, 1 H).

Example 3:

Preparation of 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole and 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-tetrazole



A suspension of magnesium turnings (2.68 g) in anhydrous tetrahydrofuran (20 ml) is cooled to 10°C and five drops of 1,2-dibromoethane are added. 2 ml of a solution of 2-(4-bromo-phenyl)-[1,3]dioxane (24.3 g; 100 mmol) in anhydrous tetrahydrofuran (80 ml) is added at 10°C under vigorous stirring. After the reaction starts the remainder of the solution of 2-(4-bromo-phenyl)-[1,3]dioxane is added over 90 minutes. The resulting mixture is further stirred at about 16°C for 2 hours and at 25°C for 75 minutes. The concentration of 4-([1,3]dioxan-2-yl)phenylmagnesium bromide in the solution above the excess of magnesium turnings is about 0.90 M. In another flask, dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (0.054 g; 0.10 mmol) is suspended in 1,2-dimethoxyethane (7.7 ml) and cooled to about 0°C before a 0.5 M solution of zinc chloride in tetrahydrofuran (1.0 ml; 0.50 mmol) and a solution of a mixture of 5-(2-chlorophenyl)-2-(tetrahydropyran-2-yl)-2H-tetrazole and 5-(2-chlorophenyl)-1-(tetrahydropyran-2-yl)-1H-tetrazole (2.65 g; 10.0 mmol) in 1,2-dimethoxyethane (2.7 ml) are added. To the vigorously

stirred resulting suspension is added at about 0°C 13.4 ml of the above 0.90 M 4-([1,3]dioxan-2-yl)phenylmagnesium bromide solution (12.0 mmol) over one hour. The resulting brown-yellow solution is allowed to warm up and further stirred at room temperature for 3 hours. The mixture is cooled to about 0°C and quenched with a 7.5 % solution of ammonium chloride in water (20 ml). The aqueous phase is separated and extracted with ethyl acetate (50 ml). The combined organic phases are washed with water (20 ml), a 7.5 % solution of sodium carbonate in water (20 ml) and water (20 ml). The combined organic phases are evaporated in vacuo. A solution of the resulting oil in a small amount of ethyl acetate is filtered and evaporated. The resulting oil is purified by column chromatography on silica gel eluting with a 1:2 mixture of ethyl acetate and hexane to afford the main isomer (N2-isomer) 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole as a colorless oil and the minor isomer (N1-isomer) 5-(4'-[1,3]dioxan-2-yl-biphenyl-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-tetrazole as colorless crystals.

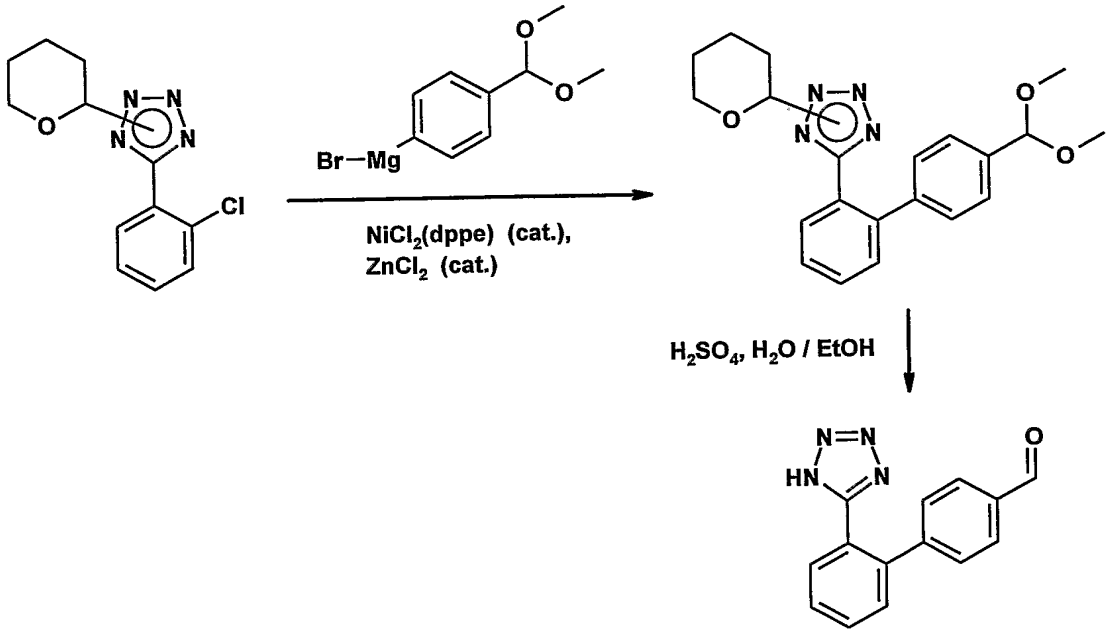
^{1}H-NMR of N2-isomer (400 MHz, $CDCl_3$): 1.42-1.47 (m, 1 H), 1.57-1.65 (m, 3 H), 1.79-1.87 (m, 1 H), 1.96-2.03 (m, 1 H), 2.10-2.27 (m, 2 H), 3.60-3.69 (m, 2 H), 3.95-4.01 (m, 2 H), 4.23-4.27 (m, 2 H), 5.48 (s, 1 H), 5.98-6.00 (m, 1 H), 7.18-7.21 (m, 2 H), 7.38-7.42 (m, 3 H), 7.46-7.54 (m, 2 H), 7.89-7.91 (m, 1 H).

^{1}H-NMR of N1-isomer (400 MHz, $CDCl_3$): 0.98-1.02 (m, 1 H), 1.31-1.36 (m, 1 H), 1.42-1.47 (m, 2 H), 1.51-1.61 (m, 1 H), 1.87-1.96 (m, 2 H), 2.14-2.26 (m, 1 H), 3.25-3.31 (m, 1 H), 3.70-3.75 (m, 1 H), 3.93-4.00 (m, 2 H), 4.22-4.27 (m, 2 H), 4.84-4.87 (m, 1 H), 5.45 (s, 1 H), 7.12-7.15 (m, 2 H), 7.40-7.42 (m, 2 H), 7.50-7.68 (m, 4 H).

Melting range of N1-isomer: 125-127°C.

Example 4:

Preparation of 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde

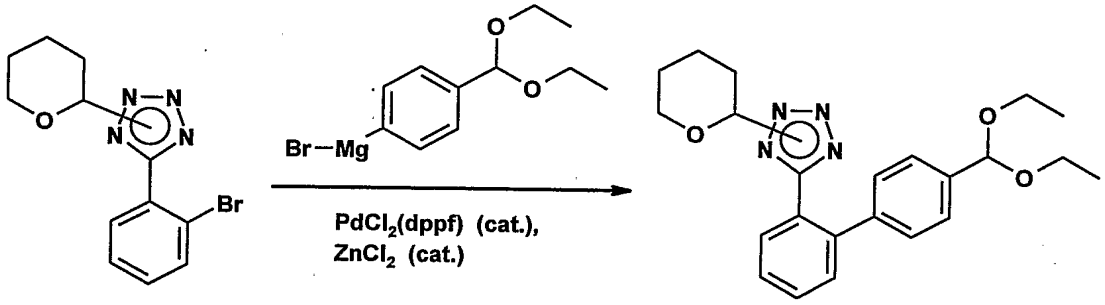


A suspension of magnesium turnings (2.35 g) in anhydrous tetrahydrofuran (66 ml) is cooled to 14°C, treated with a 1 M solution of diisobutylaluminum hydride in tetrahydrofuran (1.8 ml, 1.8 mmol) and stirred for 20 min. At 14°C, 1-bromo-4-dimethoxymethyl-benzene (1.02 g; 4.4 mmol) is added under vigorous stirring. After the reaction starts, more 1-bromo-4-dimethoxymethyl-benzene (19.32 g; 83.6 mmol) is added over 45 minutes. The resulting mixture is further stirred at about 25°C for 2.5 hours. The concentration of 4-(dimethoxymethyl)phenylmagnesium bromide in the solution above the excess of magnesium turnings is about 0.96 M. In another flask, a mixture of 5-(2-chlorophenyl)-2-(tetrahydropyran-2-yl)-2H-tetrazole and 5-(2-chlorophenyl)-1-(tetrahydropyran-2-yl)-1H-tetrazole (20.47 g; 75.0 mmol) is dissolved in anhydrous tetrahydrofuran (14 ml) under an inert atmosphere and dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) (0.404 g; 0.75 mmol) and a 0.5 M solution of zinc chloride in tetrahydrofuran (2.25 ml; 1.13 mmol) are added. The vigorously stirred resulting suspension is cooled to about 15°C and the above 0.96 M 4-(dimethoxymethyl)phenylmagnesium bromide solution (90 ml; 86.3 mmol) is added over one hour while keeping the temperature below 25°C by external cooling. The dark brown reaction mixture is agitated at room temperature for 18 hours. After that, more than 99 % of the starting material are converted and methanol (2.2 ml) is added to the mixture.

Most of the tetrahydrofuran is distilled off under reduced pressure and replaced by approximately 115 ml of ethanol. To the resulting turbid, brown solution is added at 50°C a 0.5 M aqueous solution of sulfuric acid (48 ml; 24 mmol) over 20 minutes. The mixture is further stirred at 50°C for 40 minutes and at 65°C for 2.5 hours, treated with activated carbon, stirred and filtered over filter aid at about 55°C. The yellowish filtrate is concentrated by distilling off about 62 ml of solvents under reduced pressure. After adding water (27 ml) at 60°C, the stirred resulting suspension is allowed to cool to room temperature and more water (6 ml) is added before it is further stirred at about 0°C. The solids are collected by filtration, washed with a 2 : 3 mixture of ethanol and water and water and are dried under reduced pressure at about 50°C to afford 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde as off-white crystalline solid.
Melting range: 188.5-189.5°C.

Example 5:

Preparation of 5-(4'-diethoxymethyl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole



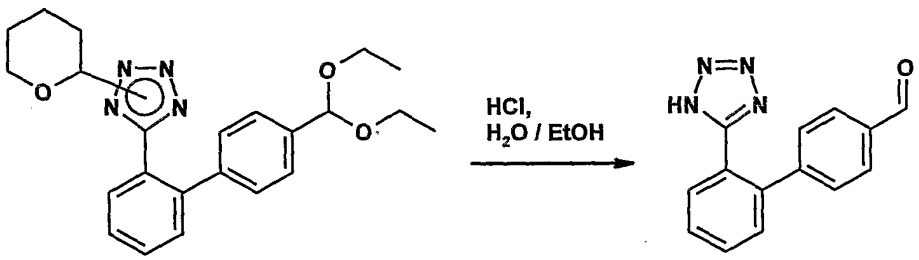
To a suspension of magnesium turnings (5.11 g) in anhydrous tetrahydrofuran (40 ml) is added 1,2-dibromoethane (0.106 ml; 1.2 mmol). The suspension is cooled to 12°C and 6 ml of a solution of 1-bromo-4-(diethoxymethyl)benzene (53.6 g; 200 mmol) in anhydrous tetrahydrofuran (120 ml) and a second portion of 1,2-dibromoethane (0.106 ml; 1.2 mmol) are added. After the reaction starts the remainder of the solution of 1-bromo-4-(diethoxymethyl)benzene is added over 90 minutes. The resulting mixture is further stirred at 20 to 25°C for 2.5 hours. The mixture is diluted with anhydrous tetrahydrofuran to a total volume of 250 ml. The concentration of 4-(diethoxymethyl)phenylmagnesium bromide in the solution above the excess of magnesium turnings is about 0.78 M. In another flask are added to dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.012 g; 0.015 mmol) a 0.5 M zinc chloride solution in tetrahydrofuran (0.6 ml; 0.30 mmol) and a solution of a mixture of 5-(2-bromophenyl)-2-(tetrahydropyran-2-yl)-2H-tetrazole

and 5-(2-bromophenyl)-1-(tetrahydropyran-2-yl)-1H-tetrazole (4.99 g; 14.3 mmol) in tetrahydrofuran (30 ml). To the stirred resulting yellow-orange solution is added at room temperature 22.2 ml of the above 0.78 M 4-(diethoxymethyl)phenylmagnesium bromide solution (17.3 mmol) over two hours. The resulting orange solution is further stirred at room temperature for 18 hours. After that, no more starting material could be detected by thin layer chromatography. The mixture is cooled to about 0°C and a solution of sodium hydrogencarbonate (2.0 g) in water (25 ml) and ethyl acetate (30 ml) are added. The aqueous phase is separated and extracted with ethyl acetate (40 ml). The combined organic phases are washed with a solution of sodium hydrogencarbonate (2.0 g) in water (25 ml) and twice with water (25 ml) before they are evaporated in vacuo. The resulting orange oil is purified by column chromatography on silica gel eluting with a 1:4 mixture of ethyl acetate and hexane (in the presence of 0.3 volume-% of triethylamine) to afford the main isomer (N2-isomer) 5-(4'-diethoxymethyl-biphenyl-2-yl)-2-(tetrahydro-pyran-2-yl)-2H-tetrazole as a pale yellow oil.

^{1}H-NMR of N2-isomer (400 MHz, $CDCl_3$): 1.24 (t, J = 7.2 Hz, 6 H), 1.59-1.67 (m, 3 H), 1.85-2.03 (m, 2 H), 2.11-2.18 (m, 1 H), 3.50-3.74 (m, 6 H), 5.49 (s, 1 H), 5.97-5.99 (m, 1 H), 7.17-7.20 (m, 2 H), 7.38-7.40 (m, 2 H), 7.43-7.56 (m, 3 H), 7.90-7.92 (m, 1 H).

Example 6:

Preparation of 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde

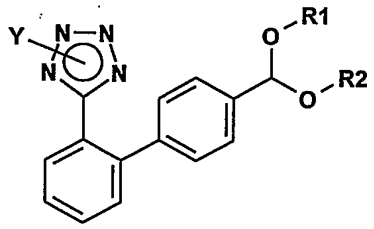


To 5-(4'-diethoxymethyl-biphenyl-2-yl)-2-(tetrahydropyran-2-yl)-2H-tetrazole (0.408 g; 1.00 mmol) are added 94 % ethanol (2.5 ml) and a 2N aqueous solution of hydrochloric acid (0.5 ml; 1.0 mmol). The resulting solution is heated to 45°C for 3 hours. After the addition of water (about 2 ml) the mixture is allowed to cool down to room temperature and then stirred at 0 to 5°C for 30 minutes. The resulting suspension is filtered and the solids are washed with a small amount of water, dried in vacuo at 40°C to afford 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde as white, crystalline powder.

Melting point: 187.5-190.0°C.

What is claimed is

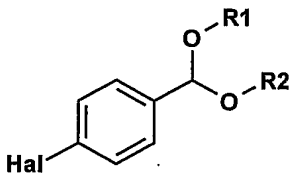
1. A process for the manufacture of the compound of formula (I) .



(I),

wherein Y represents a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene; comprising

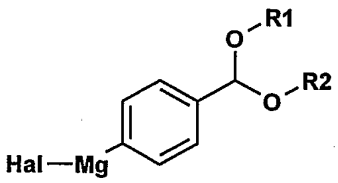
(a) reacting a compound of formula



(II a)

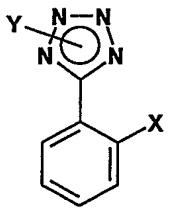
wherein Hal is chlorine, bromine or iodine, with an active form of magnesium in an appropriate solvent

(b) reacting a resulting aryl magnesium halide compound of formula



(II b)

in the presence of a transition metal catalyst and in the presence of a catalytically effective amount of a metal salt additive with a compound of formula (II c)



(II c),

wherein X is a substituent which, when bound to a phenyl ring, is not considerably replaceable at room temperature by an arylmagnesium halide reagent of formula (II b) in the absence of a catalyst; and, if necessary,

isolating a resulting compound of formula (I).

2. Process according to claim 1, wherein variable Y is selected from the group consisting of tert-butyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, 1-methyl-1-phenylethyl, triphenylmethyl, (p-methoxyphenyl)-diphenylmethyl, benzyloxymethyl, methoxymethyl, methoxy-1-methylethyl, 1-methoxycyclohexyl, 1-ethoxycyclohexyl, trimethylsilyl and triethylsilyl.

3. Process according to claim 1 or 2, wherein a transition metal catalyst is selected from the group consisting of nickel, palladium, platinum, cobalt, manganese or copper and wherein a useful transition metal salt is selected from the group consisting of a nickel(II), palladium(II), platinum(II), cobalt(II), manganese(II), copper(I) or copper (II) salt such as the chloride, bromide, iodide, hydroxide, oxide, acetate, hydroxyacetate, propionate, succinate, trifluoroacetate, acetylacetonate, nitrate, cyanide, sulfate, trifluoromethanesulfonate, methanesulfonate, benzenesulfonate or p-toluenesulfonate thereof.

4. Process according to any one of claims 1 to 3, wherein a suitable transition metal catalyst is a complex of a transition metal or a transition metal salt and one, two or up to four coordinating ligants selected from the group consisting of

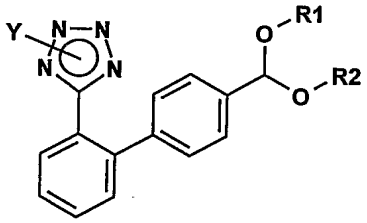
5. Process according to any one of claims 1 to 4, wherein a metal salt additive is selected from the group consisting of a copper(I), copper(II), zinc(II), silver(I), cadmium(II), mercury(II), aluminum(III), gallium(III), indium(III), tin(IV), titanium(IV) and zirconium(IV) salt.

6. Process according to any one of claims 1 to 5, wherein the amount of metal salt additive used is between 0.1 and 8 molar% relative to N-protected tetrazole starting material (II c), preferably between 0.5 and 6 molar%.

7. Process according to any one of claims 1 to 6, wherein, when X is chlorine, a transition metal catalyst is a nickel(0) or nickel(II) complex, for example, a complex of a nickel(II) salt which is coordinated by at least one organo phosphorus compound containing trivalent phosphorus; a nickel(II) complex comprising two organophosphorus ligands; or a nickel(II) complex with organophosphorus ligands which contain two trivalent phosphorus atoms, such as dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) (i.e. $NiCl_2$(dppe)); and a metal salt additive is a zinc(II) salt such as $ZnCl_2$ and $ZnBr_2$.

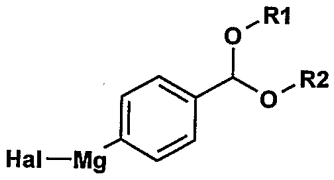
8. Process according to any one of claims 1 to 6, wherein, when X is bromine, a transition metal catalyst is a palladium complex, for example, a complex of palladium(0) or a complex of a palladium(II) salt with at least one organophosphorus compound containing trivalent phosphorus; a palladium(II) complexp comprising two organophosphorus ligands; or a palladium(II) complexes with organophosphorus ligands which contain two trivalent phosphorus atoms, such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (i.e. $PdCl_2$(dppf)) or its dichloromethane adduct; and a metal salt additive is a zinc(II) salt such as $ZnCl_2$ and $ZnBr_2$.

9. A process for the manufacture of the compound of formula (I)



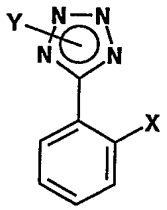
(I),

wherein Y represents a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene; comprising reacting an aryl magnesium halide compound of formula



(II b)

in the presence of a transition metal catalyst and in the presence of a catalytically effective amount of a metal salt additive with a compound of formula (II c)

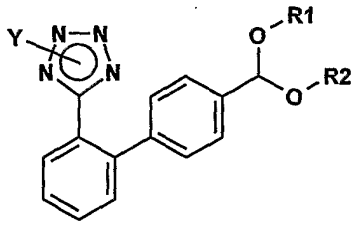


(II c),

wherein X is a substituent which, when bound to a phenyl ring, is not considerably replaceable at room temperature by an arylmagnesium halide reagent of formula (II b) in the absence of a catalyst; and, if necessary,

isolating a resulting compound of formula (I).

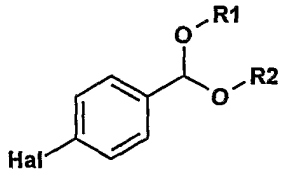
10. A process for the manufacture of the compound of formula (I)



(I),

wherein Y represents a tetrazole protecting group, and R_1 and R_2, independently of one another, represent C_1-C_{10}-alkyl or together form C_2-C_{10}-alkylene; comprising

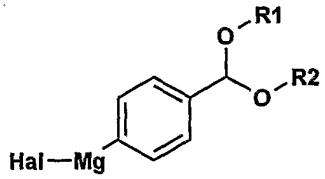
(a) reacting a compound of formula



(II a)

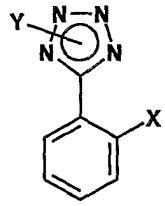
wherein Hal is chlorine, bromine or iodine, with an active form of magnesium in an appropriate solvent

(b) reacting a resulting aryl magnesium halide compound of formula



(II b)

in the presence of a transition metal catalyst with a compound of formula (II c)



(II c),

wherein X is chlorine, in the absence of a metal salt additive; and, if necessary, isolating a resulting compound of formula (I).

Abstract

~~Process for the Manufacture of Organic Compounds~~

The present invention relates to a process for the manufacture of intermediates that may be used for the manufacture of ARBs (also called angiotension II receptor antagonist or AT_1 receptor antagonist) comprising as structural feature a tetrazole ring.